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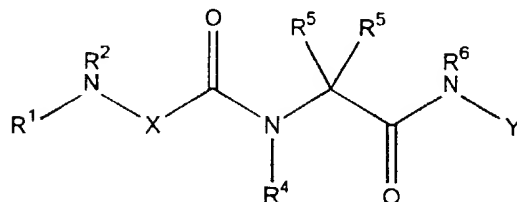
(51) International Patent Classification ⁶ : C07K 5/023, A61K 38/04, 31/47, 38/03, C07D 401/12	A2	(11) International Publication Number: WO 99/47545 (43) International Publication Date: 23 September 1999 (23.09.99)
(21) International Application Number: PCT/US99/05919 (22) International Filing Date: 19 March 1999 (19.03.99) (30) Priority Data: 60/078,770 19 March 1998 (19.03.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/078,770 (CON) Filed on 19 March 1998 (19.03.98) (71) Applicant (for all designated States except US): VERTEX PHARMACEUTICALS INCORPORATED [US/US]; 130 Waverly Street, Cambridge, MA 02139-4242 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): WANNAMAKER, Marion, W. [US/US]; 375 Harvard Road, Stow, MA 01775 (US). BEMIS, Guy, W. [US/US]; 256 Appleton Street, Arlington, MA 01572 (US). CHARIFSON, Paul, S. [US/US]; 7 Dartmouth Drive, Framingham, MA 01701 (US). LAUFFER, David, J. [US/US]; 254 Taylor Road, Stow, MA 01775 (US). MULLICAN, Michael, D. [US/US]; 110 Parker Road, Needham, MA 02194 (US). MURCKO, Mark, A. [US/US];		520 Marshall Street, Holliston, MA 01746 (US). WILSON, Keith, P. [US/US]; 6 Longwood Drive, Hopkinton, MA 01748 (US). JANETKA, James, W. [US/US]; 3612 Stearns Hill Road, Waltham, MA 02451 (US). DAVIES, Robert, J. [GB/US]; Apartment 2K, 225 Weldon Street, Cambridge, MA 02109 (US). GRILLOT, Anne-Laure [FR/US]; Apartment #3R, 31 Regent Street, Cambridge, MA 02140 (US). SHI, Zhan [CN/US]; Apartment 7, 15 Sheridan Drive, Shrewsbury, MA 01545 (US). FORSTER, Cornelia, J. [US/US]; 8 Nancy Avenue, Pelham, NH 03076 (US). (74) Agents: HALEY, James, F., Jr.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US) et al. (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: INHIBITORS OF CASPASES (57) Abstract The present invention relates to novel classes of compounds which are caspase inhibitors, in particular interleukin-1 β converting enzyme ("ICE") inhibitors. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting caspase activity and consequently, may be advantageously used as agents against interleukin-1- ("IL-1"), apoptosis-, interferon- γ inducing factor- (IGIF), or interferon- γ - ("IFN- γ ") mediated diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, and degenerative diseases. This invention also relates to methods for inhibiting caspase activity and decreasing IGIF production and IFN- γ production and methods for treating interleukin-1, apoptosis-, and interferon- γ - mediated diseases using the compounds and compositions of this invention. This invention also relates to methods of preparing the compounds of this invention.		

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What is claimed is:

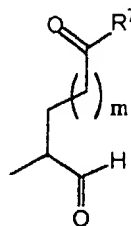
1. A compound represented by formula I:



wherein:

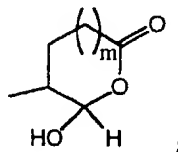
Y is:

(a)



provided that when R⁷ is -OH then Y can also be:

(b)



X is -C(R³)₂- or -N(R³)-;

m is 0 or 1;

R¹ is H, -R⁸, -C(O)R⁸, -C(O)C(O)R⁸, -S(O)₂R⁸,
 -S(O)R⁸, -C(O)OR⁸, -C(O)N(H)R⁸, -S(O)₂N(H)-R⁸,
 -S(O)N(H)-R⁸, -C(O)C(O)N(H)R⁸, -C(O)CH=CHR⁸,

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-C(O)CH₂OR⁸, -C(O)CH₂N(H)R⁸, -C(O)N(R⁸)₂, -S(O)₂N(R⁸)₂,
-S(O)N(R⁸)₂, -C(O)C(O)N(R⁸)₂, -C(O)CH₂N(R⁸)₂, -CH₂R⁸,
-CH₂-alkenyl-R⁸, or -CH₂-alkynyl-R⁸;

5 R² is -H and each R³ is independently -H, an
amino acid side chain, -R⁸, alkenyl-R⁹, or alkynyl-R⁹,
or each R³, together with the atom to which they are
bound, form a 3 to 7 membered cyclic or heterocyclic
cyclic ring system, or R² and one R³ together with the
10 atoms to which they are bound, form a 3 to 7 membered
cyclic or heterocyclic ring system, wherein a hydrogen
atom bound to any -alkyl or -cycloalkyl carbon atom is
optionally replaced by -R¹⁰, a hydrogen atom bound to
any -aryl or -heteroaryl carbon atom is optionally
15 replaced by -R¹¹, a hydrogen atom bound to any nitrogen
atom of the ring system is optionally replaced by -R¹;

 R⁴ is -H and each R⁵ is independently -H, an
amino acid side chain, -R⁸, -alkenyl-R⁹, or -alkynyl-
20 R⁹, or R⁴ and one R⁵ together with the atoms to which
they are bound form a 3 to 7 membered cyclic or
heterocyclic ring system, wherein a hydrogen atom bound
to any -alkyl or -cycloalkyl carbon atom is optionally
replaced by R¹⁰, a hydrogen atom bound to any -aryl or
25 -heteroaryl carbon atom is optionally replaced by R¹¹,
and a hydrogen atom bound to any nitrogen atom of the
ring system is optionally replaced with R¹;

 R⁶ is -H;

30

 R⁷ is -OH, -OR⁸, or -N(H)OH;

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each R⁸ is independently -alkyl, -cycloalkyl,
-aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl
-alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl,
5 wherein a hydrogen atom bound to any -alkyl or
-cycloalkyl carbon atom is optionally replaced by R¹⁰,
a hydrogen atom bound to any -aryl or -heteroaryl
carbon atom is optionally replaced by R¹¹, and a
hydrogen atom bound to any nitrogen atom is optionally
10 replaced by R¹;

each R⁹ is independently -aryl, -heteroaryl,
cycloalkyl, or -heterocyclyl, wherein a hydrogen atom
bound to any -alkyl or -cycloalkyl carbon atom is
15 optionally replaced by R¹⁰, a hydrogen atom bound to
any -aryl or -heteroaryl carbon atom is optionally
replaced by R¹¹, and a hydrogen atom bound to any
nitrogen atom is optionally replaced by R¹;

20

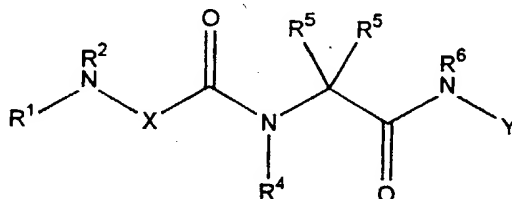
each R¹⁰ is independently -OH, -SH, -F, -Cl,
-Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H,
-N(H)C(O)NH₂, -perfluoroalkyl, -O-alkyl, -O-aryl,
-O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl,
25 -N(alkyl)₂, -C(O)N(H)alkyl, -C(O)N(alkyl)₂,
-N(H)C(O)alkyl, -N(H)C(O)Oalkyl, -N(H)C(O)Oaryl,
-N(H)C(O)Oalkylaryl, -N(H)C(O)Oheteroaryl,
-N(H)C(O)Oalkylheteroaryl, -N(H)C(O)Ocycloalkyl,
-N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)₂,
30 -N(H)C(O)N(H)aryl, -N(H)C(O)N(H)alkylaryl,
-N(H)C(O)N(H)heteroaryl, -N(H)C(O)N(H)alkylheteroaryl,
-N(H)C(O)N(H)cycloalkyl, -S-alkyl, -S-aryl,
-S-alkylaryl, -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl,
-CH₂NH₂, -CH₂N(H)alkyl, or -CH₂N(alkyl)₂, -alkyl,

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-cycloalkyl, -aryl, -heteroaryl, -heterocyclyl,
 -alkylcycloalkyl -alkylaryl, -alkylheteroaryl, or
 -alkylheterocyclyl, wherein a hydrogen atom bound to
 any -aryl or -heteroaryl carbon atom is optionally
 5 replaced by R¹¹ and a hydrogen atom bound to any
 nitrogen atom is optionally replaced by R¹; and

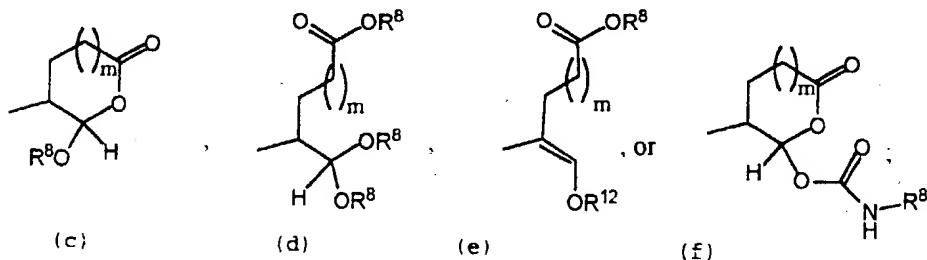
each R¹¹ is independently -OH, -SH, -F, -Cl,
 -Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H,
 10 -N(H)C(O)NH₂, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-
 alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl,
 -N(H)-alkylaryl, -N(alkyl)₂, -C(O)N(H)alkyl,
 -C(O)N(alkyl)₂, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl,
 -N(H)C(O)N(alkyl)₂, -S-alkyl, -S-aryl, -S-alkylaryl,
 15 -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl, -CH₂NH₂,
 -CH₂N(H)alkyl, or -CH₂N(alkyl)₂.

2. A compound represented by formula I:



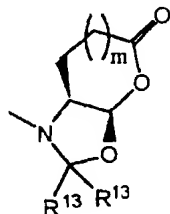
wherein:

Y is:



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provided that when R^6 is not hydrogen, R^6 and Y, together with the nitrogen to which they are bound, form a ring (g):



5 (g) ;

X is $-C(R^3)_2-$ or $-N(R^3)-$;

m is 0 or 1;

10

R^1 is H, $-R^8$, $-C(O)R^8$, $-C(O)C(O)R^8$, $-S(O)_2R^8$, $-S(O)R^8$, $-C(O)OR^8$, $-C(O)N(H)R^8$, $-S(O)_2N(H)-R^8$, $-S(O)N(H)-R^8$, $-C(O)C(O)N(H)R^8$, $-C(O)CH=CHR^8$, $-C(O)CH_2OR^8$, $-C(O)CH_2N(H)R^8$, $-C(O)N(R^8)_2$, $-S(O)_2N(R^8)_2$, $-S(O)N(R^8)_2$, $-C(O)C(O)N(R^8)_2$, $-C(O)CH_2N(R^8)_2$, $-CH_2R^8$, $-CH_2$ -alkenyl- R^8 , or $-CH_2$ -alkynyl- R^8 ;

15

R^2 is $-H$ and each R^3 is independently $-H$, an amino acid side chain, $-R^8$, alkenyl- R^9 , or alkynyl- R^9 , or each R^3 , together with the atom to which they are bound, form a 3 to 7 membered cyclic or heterocyclic cyclic ring system, or R^2 and one R^3 together with the atoms to which they are bound, form a 3 to 7 membered cyclic or heterocyclic ring system, wherein a hydrogen atom bound to any $-alkyl$ or $-cycloalkyl$ carbon atom is optionally replaced by $-R^{10}$, a hydrogen atom bound to any $-aryl$ or $-heteroaryl$ carbon atom is optionally

20

25

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replaced by $-R^{11}$, a hydrogen atom bound to any nitrogen atom of the ring system is optionally replaced by $-R^1$;

5 R^4 is $-H$ and each R^5 is independently $-H$, an amino acid side chain, $-R^8$, $-alkenyl-R^9$, or $-alkynyl-R^9$, or R^4 and one R^5 together with the atoms to which they are bound form a 3 to 7 membered cyclic or heterocyclic ring system, wherein a hydrogen atom bound to any $-alkyl$ or $-cycloalkyl$ carbon atom is optionally
10 replaced by R^{10} , a hydrogen atom bound to any $-aryl$ or $-heteroaryl$ carbon atom is optionally replaced by R^{11} , and a hydrogen atom bound to any nitrogen atom of the ring system is optionally replaced with R^1 ;

15 R^6 is $-H$;

each R^8 is independently $-alkyl$, $-cycloalkyl$, $-aryl$, $-heteroaryl$, $-heterocyclyl$, $-alkylcycloalkyl$, $-alkylaryl$, $-alkylheteroaryl$, or $-alkylheterocyclyl$, wherein a hydrogen atom bound to any $-alkyl$ or
20 $-cycloalkyl$ carbon atom is optionally replaced by R^{10} , a hydrogen atom bound to any $-aryl$ or $-heteroaryl$ carbon atom is optionally replaced by R^{11} , and a hydrogen atom bound to any nitrogen atom is optionally replaced by R^1 ;

25 each R^9 is independently $-aryl$, $-heteroaryl$, $cycloalkyl$, or $-heterocyclyl$, wherein a hydrogen atom bound to any $-alkyl$ or $-cycloalkyl$ carbon atom is optionally replaced by R^{10} , a hydrogen atom bound to
30 any $-aryl$ or $-heteroaryl$ carbon atom is optionally replaced by R^{11} , and a hydrogen atom bound to any nitrogen atom is optionally replaced by R^1 ;

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each R¹⁰ is independently -OH, -SH, -F, -Cl, -Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H, -N(H)C(O)NH₂, -perfluoroalkyl, -O-alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl, -N(alkyl)₂, -C(O)N(H)alkyl, -C(O)N(alkyl)₂, -N(H)C(O)alkyl, -N(H)C(O)Oalkyl, -N(H)C(O)Oaryl, -N(H)C(O)Oalkylaryl, -N(H)C(O)Oheteroaryl, -N(H)C(O)Oalkylheteroaryl, -N(H)C(O)Ocycloalkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)₂, -N(H)C(O)N(H)aryl, -N(H)C(O)N(H)alkylaryl, -N(H)C(O)N(H)heteroaryl, -N(H)C(O)N(H)alkylheteroaryl, -N(H)C(O)N(H)cycloalkyl, -S-alkyl, -S-aryl, -S-alkylaryl, -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl, -CH₂NH₂, -CH₂N(H)alkyl, or -CH₂N(alkyl)₂, -alkyl, -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl, -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl, wherein a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R¹¹ and a hydrogen atom bound to any nitrogen atom is optionally replaced by R¹; and

each R¹¹ is independently -OH, -SH, -F, -Cl, -Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H, -N(H)C(O)NH₂, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl, -N(alkyl)₂, -C(O)N(H)alkyl, -C(O)N(alkyl)₂, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)₂, -S-alkyl, -S-aryl, -S-alkylaryl, -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl, -CH₂NH₂, -CH₂N(H)alkyl, or -CH₂N(alkyl)₂;

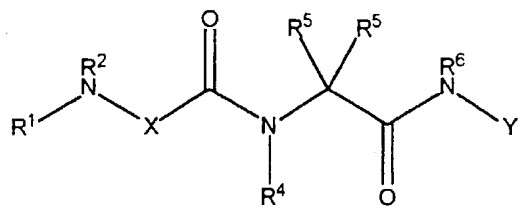
R¹² is -C(O)alkyl, -C(O)cycloalkyl, -C(O)alkenyl, -C(O)alkylaryl, -C(O)alkylheteroaryl, -C(O)heterocyclyl, or -C(O)alkylheterocyclyl; and

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R^{13} is -H, -alkyl, -aryl, -alkylaryl or -alkylheteroaryl.

5

3. A compound represented by formula 1:

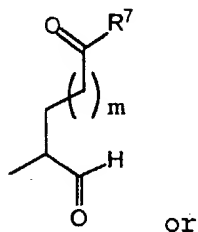


wherein:

Y is:

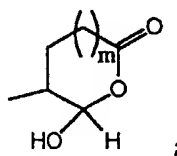
10

(a)



or

(b)



15

m is 0 or 1;

X is $-C(R^3)_2-$

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R^1 is H, $-R^8$, $-C(O)R^8$, $-C(O)C(O)R^8$, $-S(O)_2R^8$,
 $-S(O)R^8$, $-C(O)OR^8$, $-C(O)N(H)R^8$, $-S(O)_2N(H)-R^8$,
 $-S(O)N(H)-R^8$, $-C(O)C(O)N(H)R^8$, $-C(O)CH=CHR^8$,
 $-C(O)CH_2OR^8$, $-C(O)CH_2N(H)R^8$, $-C(O)N(R^8)_2$, $-S(O)_2N(R^8)_2$,
5 $-S(O)N(R^8)_2$, $-C(O)C(O)N(R^8)_2$, $-C(O)CH_2N(R^8)_2$, $-CH_2R^8$,
 $-CH_2$ -alkenyl- R^8 , or $-CH_2$ -alkynyl- R^8 ;

R^2 is -H and each R^3 is independently -H, an
amino acid side chain, $-R^8$, alkenyl- R^9 , or alkynyl- R^9 ,
10 or each R^3 together with the atom to which they are
bound, form a 3 to 7 membered cyclic or heterocyclic
ring system, wherein a hydrogen atom bound to any
-alkyl or -cycloalkyl carbon atom is optionally
replaced by $-R^{10}$, a hydrogen atom bound to any -aryl or
15 -heteroaryl carbon atom is optionally replaced by $-R^{11}$,
a hydrogen atom bound to any nitrogen atom of the ring
system is optionally replaced by $-R^1$;

R^4 is -H and each R^5 is independently -H, an
20 amino acid side chain, $-R^8$, -alkenyl- R^9 , or
-alkynyl- R^9 , or R^4 and one R^5 together with the atoms
to which they are bound form a 3 to 7 membered cyclic
or heterocyclic ring system, wherein a hydrogen atom
bound to any -alkyl or -cycloalkyl carbon atom is
25 optionally replaced by R^{10} , a hydrogen atom bound to
any -aryl or -heteroaryl carbon atom is optionally
replaced by R^{11} , and a hydrogen atom bound to any
nitrogen atom of the ring system is optionally replaced
with R^1 ;

30

R^6 is -H;

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R⁷ is -OH, -OR⁸, -N(H)OH, or -N(H)S(O)₂R⁸;

each R⁸ is independently -alkyl, -cycloalkyl,
5 -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl
-alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl,
wherein a hydrogen atom bound to any -alkyl or
-cycloalkyl carbon atom is optionally replaced by R¹⁰,
a hydrogen atom bound to any -aryl or -heteroaryl
10 carbon atom is optionally replaced by R¹¹, and a
hydrogen atom bound to any nitrogen atom is optionally
replaced by R¹;

each R⁹ is independently -aryl, -heteroaryl,
15 cycloalkyl, or -heterocyclyl, wherein a hydrogen atom
bound to any -alkyl or -cycloalkyl carbon atom is
optionally replaced by R¹⁰, a hydrogen atom bound to
any -aryl or -heteroaryl carbon atom is optionally
replaced by R¹¹, and a hydrogen atom bound to any
20 nitrogen atom is optionally replaced by R¹;

each R¹⁰ is independently -OH, -SH, -F, -Cl,
-Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H,
-N(H)C(O)NH₂, -perfluoroalkyl, -O-alkyl, -O-aryl,
25 -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl,
-N(alkyl)₂, -C(O)N(H)alkyl, -C(O)N(alkyl)₂,
-N(H)C(O)alkyl, -N(H)C(O)Oalkyl, -N(H)C(O)Oaryl,
-N(H)C(O)Oalkylaryl, -N(H)C(O)Oheteroaryl,
-N(H)C(O)Oalkylheteroaryl, -N(H)C(O)Ocycloalkyl,
30 -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)₂,
-N(H)C(O)N(H)aryl, -N(H)C(O)N(H)alkylaryl,
-N(H)C(O)N(H)heteroaryl, -N(H)C(O)N(H)alkylheteroaryl,
-N(H)C(O)N(H)cycloalkyl, -S-alkyl, -S-aryl,
-S-alkylaryl, -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl,

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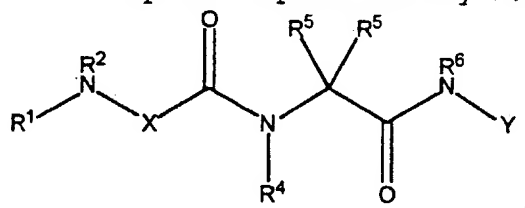
-CH₂NH₂, -CH₂N(H)alkyl, or -CH₂N(alkyl)₂, -alkyl, -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl, wherein a hydrogen atom bound to
 5 any -aryl or -heteroaryl carbon atom is optionally replaced by R¹¹ and a hydrogen atom bound to any nitrogen atom is optionally replaced by R¹; and

each R¹¹ is independently -OH, -SH, -F, -Cl,
 10 -Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H, -N(H)C(O)NH₂, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl, -N(alkyl)₂, -C(O)N(H)alkyl, -C(O)N(alkyl)₂, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl,
 15 -N(H)C(O)N(alkyl)₂, -S-alkyl, -S-aryl, -S-alkylaryl, -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl, -CH₂NH₂, -CH₂N(H)alkyl, or -CH₂N(alkyl)₂;

provided that if one R³ is -H, then the other R³ is not -H.

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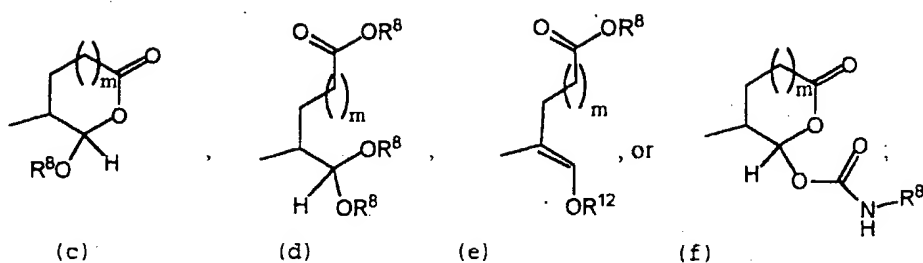
4. A compound represented by formula I:



wherein:

25 Y is:

- 284 -



m is 0 or 1;

5 X is $-C(R^3)_2-$

R^1 is H, $-R^8$, $-C(O)R^8$, $-C(O)C(O)R^8$, $-S(O)_2R^8$,
 $-S(O)R^8$, $-C(O)OR^8$, $-C(O)N(H)R^8$, $-S(O)_2N(H)-R^8$,
 $-S(O)N(H)-R^8$, $-C(O)C(O)N(H)R^8$, $-C(O)CH=CHR^8$,
 10 $-C(O)CH_2OR^8$, $-C(O)CH_2N(H)R^8$, $-C(O)N(R^8)_2$, $-S(O)_2N(R^8)_2$,
 $-S(O)N(R^8)_2$, $-C(O)C(O)N(R^8)_2$, $-C(O)CH_2N(R^8)_2$, $-CH_2R^8$,
 $-CH_2$ -alkenyl- R^8 , or $-CH_2$ -alkynyl- R^8 ;

R^2 is $-H$ and each R^3 is independently $-H$, an
 15 amino acid side chain, $-R^8$, alkenyl- R^9 , or alkynyl- R^9 ,
 or each R^3 together with the atom to which they are
 bound, form a 3 to 7 membered cyclic or heterocyclic
 ring system, wherein a hydrogen atom bound to any
 $-alkyl$ or $-cycloalkyl$ carbon atom is optionally
 20 replaced by $-R^{10}$, a hydrogen atom bound to any $-aryl$ or
 $-heteroaryl$ carbon atom is optionally replaced by $-R^{11}$,
 a hydrogen atom bound to any nitrogen atom of the ring
 system is optionally replaced by $-R^1$;

25 R^4 is $-H$ and each R^5 is independently $-H$, an
 amino acid side chain, $-R^8$, $-alkenyl-R^9$, or
 $-alkynyl-R^9$, or R^4 and one R^5 together with the atoms